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REVIEW

Endoplasmic reticulum stress in liver diseases

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Abstract

The endoplasmic reticulum (ER) is an intracellular organelle that fosters the correct folding of linear polypeptides and proteins, a process tightly governed by the ER-resident enzymes and chaperones. Failure to shape the proper 3-dimensional architecture of proteins culminates in the accumulation of misfolded or unfolded proteins within the ER, disturbs ER homeostasis, and leads to canonically defined ER stress. Recent studies have elucidated that cellular perturbations, such as lipotoxicity, can also lead to ER stress. In response to ER stress, the unfolded protein response (UPR) is activated to reestablish ER homeostasis ("adaptive UPR"), or, conversely, to provoke cell death when ER stress is overwhelmed and sustained ("maladaptive UPR"). It is well documented that ER stress contributes to the onset and progression of multiple hepatic pathologies including NAFLD, alcohol-associated liver disease, viral hepatitis, liver ischemia, drug toxicity, and liver cancers. Here, we review key studies dealing with the emerging role of ER stress and the UPR in the pathophysiology of liver diseases from cellular, murine, and

Abbreviations: ACTA2, actin α2, smooth muscle; AKT1, AKT serine/threonine kinase 1; ATF, activating transcription factor; BAX, BCL2 associated X, apoptosis regulator; BCL2, BCL2 apoptosis regulator; BI-1, Bax inhibitor-1; BiP, binding immunoglobulin protein; CASP, caspase; CD, cluster of differentiation; CHOP, C/EBP homologous protein; DDIT3, DNA damage inducible transcript 3; EIF2AK3, eukaryotic translation initiation factor 2 alpha kinase 3; ERAD, ER-associated degradation; ERN1, endoplasmic reticulum to nucleus signaling 1; EV, extracellular vesicle; FFA, free fatty acid; HBx, HBV x protein; HFD, high-fat diet; HNRNPA1, heterogeneous nuclear ribonucleoprotein A1; HSP70, heat shock protein family A [Hsp70] member 2; HSPA5, heat shock protein family A [Hsp70] member 5; I/R, ischemia/reperfusion; IRE1, inositol-requiring enzyme 1; IRF3, interferon regulatory factor 3; LAMP2, lysosomal associated membrane protein 2; MAP3K5, mitogen-activated protein kinase kinase kinase 5; MAPK, mitogen-activated protein kinase; MYC, MYC proto-oncogene, BHLH transcription factor; NNMT, nicotinamide N-methyltransferase; NSAIDs, nonsteroidal anti-inflammatory drugs; PBA, phenylboronic acid; PERK, protein kinase R-like endoplasmic reticulum kinase; PFOA, perfluorooctanoic acid; PLAU, plasminogen activator, urokinase; PMF, portal myofibroblast; PRKAA2/AMPK, protein kinase AMP-activated catalytic subunit α2; RACK1, receptor for activated C kinase 1; RIDD, regulated IRE1α dependent decay; SIDT2, SID1 transmembrane family member 2; SIRT, sirtuin; SMAD2, SMAD family member 2; SREBP, sterol regulatory element binding protein; TLR, toll-like receptor; TNFSF10, TNF superfamily member 10; TUDCA, tauroursodeoxycholic acid; UPR, unfolded protein response; XBP1, X-box binding protein 1; XBP1s, spliced XBP1 protein.

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human models. Specifically, we will summarize current available knowledge on pharmacological and non-pharmacological interventions that may be used to target maladaptive UPR for the treatment of nonmalignant liver diseases.

INTRODUCTION: ER STRESS AND CANONICAL UNFOLDED PROTEIN RESPONSE ACTIVATION

The endoplasmic reticulum (ER) constitutes one of the largest subcellular compartments and mediates a cadre of biological functions including cytosolic co-translational folding of proteins, Ca^{2+} homeostasis, and biosynthesis of steroids/lipids.[1] The ER serves as a network for vesicular transport including trafficking of endosomes.[2] ER function is tightly orchestrated by essential regulatory factors such as protein oxidoreductase chaperones, proteolysis/glycosylation/sulfation enzymes, Ca^{2+} transporters, and channels. Both physiological and pathological stimuli, such as B cell maturation, glucose-induced insulin secretion, nutrient deprivation, oxidative stress, hypoxia, and ER-relevant gene mutations, may all perturb ER homeostasis, resulting in ER stress.[3] In response to ER stress, eukaryotic cells have adapted the ER-nucleus signaling system, commonly known as the "unfolded protein response" (UPR) to resolve ER stress or execute cell death. Following mild to moderate ER stress, UPR is initiated to remove unfolded/misfolded proteins and restore ER homeostasis. This type of UPR is referred to as "adaptive/cytoprotective" UPR. However, after severe or persistent ER stress, UPR is overwhelmingly hyperactivated, leading to the activation of intrinsic apoptotic machinery.[4] This type of UPR is referred to as "maladaptive/unchecked/terminal" UPR.[5] Recent studies have demonstrated that UPR sensors can be turned on by stimuli that do not directly affect protein folding, such as saturated free fatty acids (FFAs), leading to the evolution of the term "canonical UPR," which refers to the activation of the three UPR sensors following buildup of unfolded/misfolded proteins.[6] Accumulating evidence indicates that severe ER stress and maladaptive UPR contribute to the pathogenesis of hepatic pathologies,[7] including dysmetabolism, acute and chronic viral infection, drug toxicity, and cancer.[8] Hence, a better comprehension of UPR mechanisms in the pathogenesis of these conditions may help in the identification of novel therapeutic strategies. This review discusses some of the recent insights into ER stress and UPR signaling in hepatic pathophysiology.

MECHANISMS OF UPR SIGNALING AND ACTIVATION

UPR signaling is initiated by three ER transmembrane proteins commonly referred to as UPR branches/sensors including protein kinase R-like endoplasmic reticulum kinase (PERK; encoded by eukaryotic translation initiation factor 2 alpha kinase 3 [*EIF2AK3*]), inositol-requiring enzyme 1 (IRE1α; encoded by endoplasmic reticulum to nucleus signaling 1 [*ERN1*]), and activating transcription factor 6 (ATF6α) (Figures 1 and 2). Under physiological conditions, the luminal domains of UPR sensors interact with and bind to the ER-resident chaperones, in particular binding immunoglobulin protein (BiP)/78-kDa glucose regulated protein (GRP78) (encoded by heat shock protein family A [Hsp70] member 5 [*HSPA5*]). When unfolded/misfolded proteins accumulate within the ER lumen, they bind to (and saturate) BiP, thus competitively dissociating BiP from luminal domains of UPR sensors, leading to their subsequent oligomerization and activation. Several lines of evidence have also suggested a direct binding of unfolded/misfolded proteins

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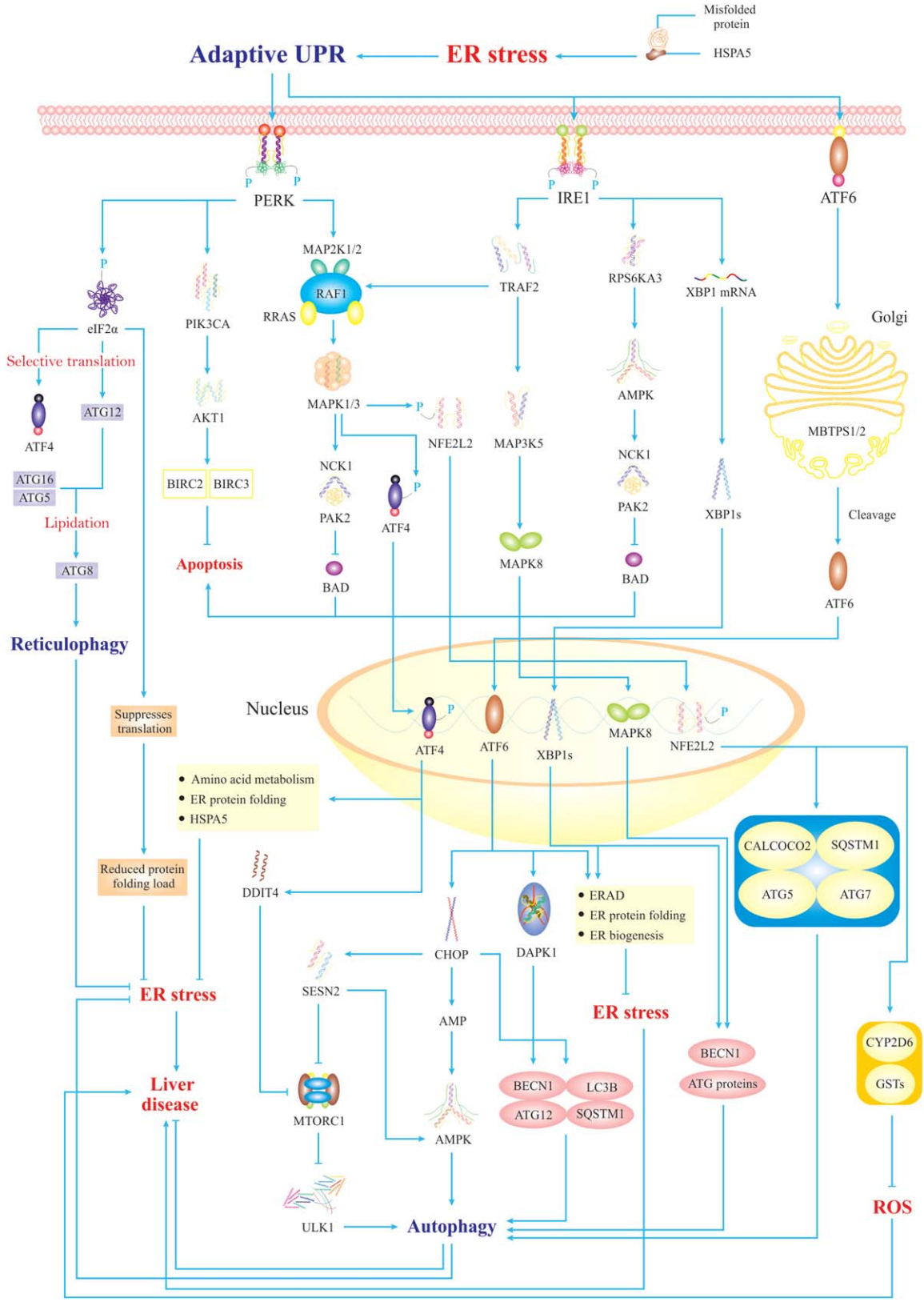

with the luminal domains of UPR sensors that result in their activation and oligomerization. In contrast, under lipotoxic conditions, IRE1α and PERK can be activated through their transmembrane domains.[9]

IRE1 branch

UPR signaling through IRE1 is highly conserved in eukaryotic cells.[10] The mammalian genome encodes

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FIGURE 1 Mild endoplasmic reticulum (ER) stress triggers adaptive unfolded protein response (UPR) signaling consist of three main branches including protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6α). PERK mediates phosphorylation of eukaryotic translation initiation factor 2 (eIF2α), which participates in autophagy of the ER (reticulophagy) through a selective translation of autophagy-related 12. In addition, PERK mediates selective translation of activating transcription factor 4 (ATF4), which translocates to the nucleus and transactivates UPR target genes associated with autophagy induction and alleviation of ER stress. Moreover, PERK activates the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA)–AKT serine/threonine kinase 1 (AKT1) axis to suppress apoptosis. Moreover, PERK turns on mitogen-activated protein kinase (MAPK) signaling, which inhibits BCL2-associated agonist of cell death (BAD)–mediated apoptosis, and activates nuclear factor, erythroid 2 like 2 (NFE2L2) that translocates to the nucleus and transactivates genes associated with autophagy and reactive oxygen species (ROS) inhibition. Similarly, IRE1 triggers pathways to block BAD-mediated apoptosis. Importantly, IRE1 induces activation of MAPK8, which translocates to the nucleus and up-regulates autophagy genes. Likewise, IRE1-activated spliced X-box binding protein 1 (XBP1s) translocates to the nucleus and transactivates autophagy and ER-associated degradation (ERAD)–related genes. Finally, activating transcription factor 6 (ATF6α) is cleaved and activated in the Golgi then translocates to the nucleus to mildly up-regulate C/EBP homologous protein (CHOP), resulting in mild autophagy. It is noteworthy that Unc-51 like autophagy activating kinase 1 (ULK1) forms an autophagy initiation complex, which is regulated by mechanistic target of rapamycin kinase (MTORC1), as ULK1 phosphorylation renders ULK1 inactivation and autophagy inhibition.[5] HSPA5, heat shock protein family A [Hsp70] member 5.

two isoforms of IRE1: IRE1α (*ERN1)* and IRE1β (*ERN2*). IRE1α and IRE1β possess different functions due to distinct RNase domains and substrate specificities. IRE1α is ubiquitously expressed and mediates downstream signaling through its kinase and endoribonuclease cytosolic domains. The role of IRE1α is well-established in UPR signaling and will be our focus in the subsequent sections. IRE1β is uniquely expressed in intestinal epithelial cells, and it is assumed that IRE1β-mediated RNA cleavage participates in digestive tissue-specific UPR.[11,12] Under normal protein load in the ER, IRE1α activation is constrained by BiP as described previously. Following the dissociation of BiP, IRE1α undergoes oligomerization and autophosphorylation.[13] IRE1α autophosphorylation activates its endoribonuclease domain to excise a 26 base intron from X-box binding protein 1 (XBP1) mRNA, leading to XBP1 splicing into the shorter XBP1 mRNA, mediated by RNA 2′,3′-cyclic phosphate and 5′-OH ligase (RtcB) RNA ligase.[14] As a result, translation of shorter XBP1 mRNA yields active spliced XBP1 protein (XBP1s) (Figures 1 and 2), which traffics to the nucleus to transactivate ER chaperones and ER secretory genes.[15] Moreover, XBP1s transactivates genes involved in ER-associated degradation (ERAD), which boosts the transport of unfolded/misfolded proteins out of ER for degradation by proteasomes.[16] In addition, the IRE1α endoribonuclease can degrade nonessential microRNAs and mRNA in a process known as "regulated IRE1α dependent decay" (RIDD).[17–19] RIDD is increasingly associated with cell survival and cell death as well as metabolic anomalies in the liver (discussed in subsequent sections).[17–19]

PERK branch

PERK is a transmembrane protein with its cytosolic kinase domain activated by oligomerization upon ER stress. The major substrate of PERK is the α subunit of the heterotrimeric eukaryotic translation initiation factor 2 (eIF2α), which may also be phosphorylated by three additional eIF2α kinases, heme-regulated inhibitor of mRNA translation (HRI), general control of nitrogen metabolism (GCN2) and double-stranded RNA activated protein kinase (PKR), which respond to different stress stimuli. This regulation couples the rate of protein synthesis to environmental factors such as viral infection (PKR), amino acid starvation (GCN2), and oxidative stress (HRI). PERK-mediated eIF2α phosphorylation leads to the general suppression of translation while allowing selective translation of certain mRNAs, such as activating transcription factor 4 (*ATF4*) mRNA.[20] ATF4 traffics to the nucleus to transactivate UPR target genes, leading to either cell survival or cell death. C/EBP homologous protein (CHOP) is considered one of the most critical and essential proapoptotic factors downstream of eIF2α and ATF4 and contributes to the pathogenesis of liver diseases[21,22] (Figures 1 and 2).

ATF6 branch

ATF6 is a transmembrane protein with a cytosolic bZIP transcription factor dimerization domain. Two mammalian paralogues, ATF6α and ATF6β, exist and contain distinct transcriptional activation domains. It is suggested that ATF6β may function as a repressor to regulate the duration and extent of ATF6α-mediated gene modulation in UPR.[23] Following ER stress, BiP releases ATF6α from the ER, enabling ATF6α to traffic to the cis-Golgi.[24] There, full-length ATF6α is cleaved into ATF6p50 by two Golgi-resident processing enzymes, namely membrane bound transcription factor peptidase, site 1 (MBTP/S1P) and membrane bound transcription factor peptidase, site 2 (MBTP/S2P), the same enzymes required for processing the liver-specific regulators of lipid homeostasis: sterol regulatory element binding protein (SREBP) 1/3, and SREBP2. Following proteolytic cleavage, the active form of ATF6α (ATF6p50) traffics to the nucleus and transactivates the UPR target genes. Moreover, ATF6p50 can heterodimerize with XBP1s, favoring up-regulation of ERAD-associated genes[24] (Figures 1 and 2).

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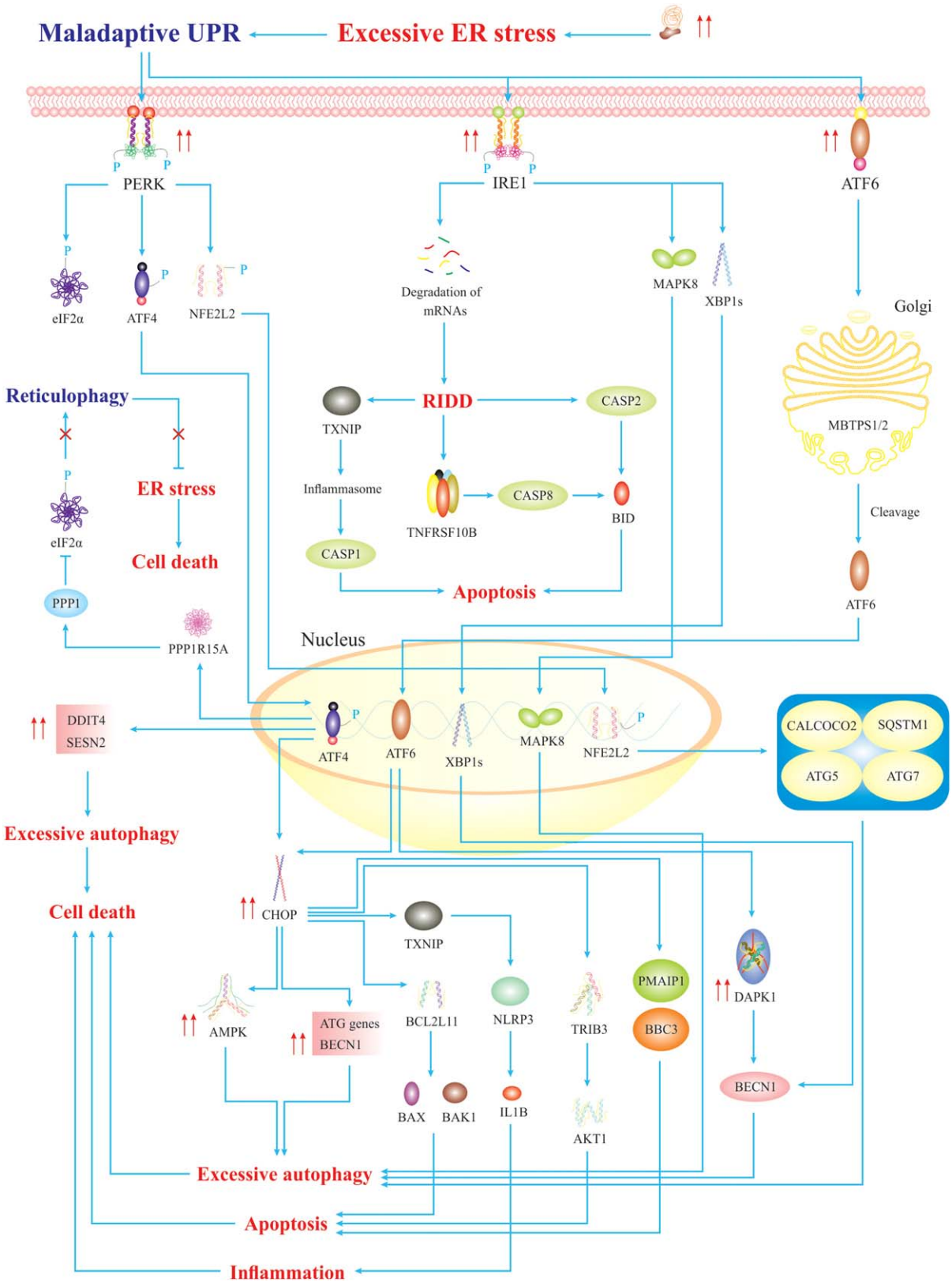

FIGURE 2 Severe ER stress triggers maladaptive UPR, leading to activation of cell death. Hyperactivated PERK triggers overexpression of NFE2L2/ATF4-target genes, leading to excessive autophagy, cell death, and CHOP-mediated apoptosis. Also, hyperactivation of IRE1 induces apoptosis through caspase 2 (CASP2) activation. Hyperactivated MAPK8 and XBP1s induce overexpression of autophagy genes, resulting in excessive autophagy. Similarly, hyperactivation of ATF6α induces overexpression of proapoptotic factors and autophagy genes, ultimately leading to cell death.[5]

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Crosstalk among UPR Branches

A possible crosstalk among IRE1α, PERK, and ATF6 in UPR activation is rather intricate. It was reported that ablation of *ATF6* evoked uncontrolled activity of IRE1α and up-regulated *XBP1* splicing.[25] In addition, cells with *ATF6* ablation exhibited temporary up-regulation of *IRE1* and IRE1 protein levels following ER stress, indicating a unique accelerated role for IRE1α signaling in the absence of ATF6. Vice versa, *ATF6* overexpression reversed the enhanced activity and levels of IRE1α.[25] Moreover, activation of the PERK-eIF2α-ATF4 axis jacked up ATF6 and its target genes. Indeed, the PERK signaling axis fostered the synthesis and translocation of ATF6 to the Golgi for ultimate activation.[26] Interestingly, a novel crosstalk between XBP1-ATF6 and PERK branches was identified in a recent study, in which PERK-mediated activation and phosphorylation of eIF2α suppressed certain subset of genes pertaining to XBP1-ATF6 signaling, thus governing cell fate and survival.[27] Moreover, it is postulated that ER stress–induced apoptosis is characterized by concerted timing of various UPR branches rather than input from a single branch or a switch between branches.[28]

ER STRESS IN NAFLD AND NASH

NAFLD is characterized by the accumulation of triglycerides in the liver, as often seen in overweight or obese individuals. A subset of patients with NAFLD develop liver injury, inflammation and fibrosis, collectively termed as NASH.[29,30] ER stress and UPR sensors are involved in steatosis, inflammation, and fibrosis in the context of NAFLD. Initial findings noted a close tie between obesity-induced ER stress and insulin resistance.[31] These initial observations were later supported by several studies elucidating the role of ER stress and UPR sensors in hepatic steatosis and individual liver cell types (cited in later sections). We discuss these further in the context of each of the UPR sensors.

IRE1α in NAFLD/NASH

IRE1α signaling through XBP1 generation and RIDD are both implicated in NAFLD.[32] Several observations support a harmful role for IRE1α activation in NASH. For example, the ER-resident protein Bax inhibitor-1 (BI-1) constrains IRE1α activation. When BI-1 is deleted, mice are sensitive to high-fat diet (HFD)–induced NASH along with increased activation of IRE1α and XBP1. Up-regulation of BI-1 inhibits IRE1α activity, leading to reduced levels of XBP1s in animal models of tunicamycin-induced ER stress.[33] Activated IRE1α promotes transcription of serine palmitoyltransferase genes via XBP1s, resulting in ceramide biosynthesis and release of extracellular vesicles (EVs) from hepatocytes.[33] In mice with diet-induced NASH, Evs recruit macrophages to the liver to accentuate inflammation and injury in diet-mediated steatohepatitis. Levels of XBP1, serine palmitoyltransferase, and Evs are all elevated in liver tissues from patients with NASH.[33] In contrast, S-nitrosylation of IRE1α resulted in reduced endoribonuclease activity of hepatic IRE1α, and thereby reduced XBP1 splicing in HFD-fed and ob/ob mice.[34,35] Nonetheless, re-initiation of hepatic IRE1α expression by establishing IRE1α resistant to s-nitrosylation culminated in increased XBP1 levels, thus augmenting glucose homeostasis.[34] Additional parameters relevant to NAFLD were not reported in this study. However, in a separate study, Wang et al. revealed an increase in liver triglyceride levels due to s-nitrosylation of IRE1α and damaged endoribonuclease activity, which inhibited IRE1α-induced degradation of *miR-34* and *miR-200*, key microRNAs that regulate hepatic lipid metabolism.[36] Moreover, this group revealed that liver-specific knockout of *IRE1a* resulted in enhanced liver fibrosis and inflammation in mice under HFD, suggesting the protective role of IRE1α against NASH.[35,36] These differences in the role of IRE1α may be partly explained by context-dependent signaling, such that a balance of XBP1 splicing and RIDD determines the eventual outcome of IRE1α activation. The possibility of additional regulatory molecules, similar to BI-1, cannot be excluded either.

PERK pathway in NAFLD/NASH

The PERK-eIF2α pathway leads to the up-regulation of UPR target genes and induces the proapoptotic protein CHOP (Figure 1). Novoa et al. revealed that growth arrest and DNA damage inducible protein 34 (GADD34) binds to protein phosphatase 1 catalytic subunit, leading to eIF2α dephosphorylation and attenuated levels of DNA damage inducible transcript 3 (*DDIT3*) and *ATF4*, thus suppressing the UPR.[37] Li et al. established HFD-induced obesity in *C57BL/6* mice and administered salubrinal (which indirectly blocks eIF2α by inhibiting its α-subunit dephosphorylation) s.c., before evaluation of autophagy and ER stress *in vitro* and *in vivo*. Histological analyses revealed that salubrinal alleviated obesity in association with reduction in hepatic steatosis and fibrosis. HFD did not induce eIF2α phosphorylation, while a rise in ATF4 was paradoxically associated with dampened *DDIT3* expression in this model, suggesting an alternative mechanism of action. Indeed, eIF2α phosphorylation induced autophagy, which might be the likely mechanism for hepato-protective effects of salubrinal.[38] However, ER stress–induced cell death

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is attenuated in CHOP-deficient hepatocytes. The role of CHOP in NASH is more complex, as CHOP-dependent macrophage apoptosis was found to protect mice from NASH.[22]

ATF6α in NAFLD/NASH

Decreased ER membrane fluidity can selectively activate ATF6α and cause NASH.[39] Recently, ATF6α was shown to be activated by sphingolipids such as dihydrosphingosine and dihydroceramide through a mechanism distinct from protein misfolding. Sphingolipid activation does not induce UPR genes, but rather turns on ER lipid biosynthetic genes.[40] ATF6p50 may indirectly suppress lipogenic genes by inducing CHOP through its dominant-negative inhibition of C/EBPα, ultimately reducing fatty acid oxidation, lipoprotein secretion, or BiP, the overexpression of which inhibits sterol regulatory element binding protein 1 (SREBP1) proteolytic cleavage.[41,42]

Secondary UPR activation in NAFLD/NASH

In addition to the these described roles of each UPR sensor in NAFLD, several studies have placed ER stress activation downstream of perturbations, which modulate lipotoxicity and NAFLD. For example, mice deficient in the lysosomal membrane protein SID1 transmembrane family member 2 (SIDT2) developed liver injury and altered lipid metabolism, causing hepatic steatosis, and inflammatory infiltration in lobular and portal areas. *SIDT2* deficiency caused significant elevation of SREBP1 protein and sterol regulatory element binding transcription factor 1 (*SREBF1*) mRNA levels, as well as up-regulation of genes implicated in fatty acid biosynthesis. Importantly, SIDT2 deficiency induced unchecked ER stress and UPR activation accompanied by ER damage in the liver.[43] Kim et al. demonstrated that ER stress–induced up-regulation of caspase 2 (CASP2) led to the accumulation of triglycerides and free cholesterol in hepatocytes by activating SREBP1/2 transcriptional factors in a diet-induced model of NASH.[44] The underlying mechanism behind SREBP1/2 activation involves colocalization of CASP2 with MBTPS1 before cleavage of MBTPS1 into a soluble active form, which in turn truncates the ER loop in SREBP1/2.[44] Consequently, SREBP1 up-regulates genes associated with fatty acid synthesis, and SREBP2 up-regulates genes in cholesterol synthesis, leading to NASH progression. In addition, pharmacological inhibition or genetic ablation of CASP2 reversed ER stress–induced NASH.[44] Excess cholesterol-activated ER stress in macrophages plays a role in atherosclerosis.[45] Similarly, in a dietary NASH model with high cholesterol (2%), accumulation of cholesterol was associated with ER stress and inflammasome activation.[46] Although the high cholesterol content limits wider generalization, these observations suggest that lipotoxicity may mediate activation of the ER stress response in models that interfere with lipid metabolism and lead to the accumulation of bioactive lipid species.

Nutrient-dependent metabolic regulators may link gene expression with ER stress. In this context, Shin et al. noted that sirtuin 7 (SIRT7) modulated gene expression, leading to reduced ER stress and NAFLD pathology in obese mice. The possible underlying mechanism was that induction of ER stress elicits SIRT7 activation, which directly inhibits MYC proto-oncogene, BHLH transcription factor (MYC) transcriptional factor to silence gene expression and relieve ER stress.[47] These authors indicated that MYC is likely to stabilize SIRT7 at the promoters of ribosomal proteins to mediate chromatin remodeling and gene repression, leading to suppression of both ER stress–associated genes and ER stress. In addition, *SIRT7* deficiency potentiated chronic hepatosteatosis, while pharmacological inhibition of ER stress or MYC inactivation mitigated ER stress and murine fatty liver.[47] This finding suggests that therapeutic targeting of the SIRT7-MYC axis could revert ER stress and murine fatty liver.

Overall, ER stress and the UPR play a cardinal role in the pathogenesis of NAFLD/NASH. Mild ER stress triggers an adaptive UPR pathway that alleviates the disease pathology, while severe and sustained ER stress leads to overwhelmed UPR activation, resulting in exacerbation of disease pathology through inflammation, cell death, and EV secretion.

ER STRESS AND ALCOHOL-ASSOCIATED LIVER DISEASE

PERK in alcohol-associated liver disease

Of the three UPR sensors, the PERK signaling pathway is most well-studied in the context of alcohol-associated liver disease (ALD). Alcohol feeding in mice fostered PERK activation and ATF4-dependent up-regulation of nicotinamide N-methyltransferase (NNMT), a key cytosolic methyltransferase enzyme, in association with up-regulation of lipogenesis genes and steatosis in ALD. Up-regulation of NNMT was dependent on *ATF4*, as ATF4 knockout reverted NNMT up-regulation.[48] This study suggests that the PERK-ATF4-NNMT axis up-regulates *de novo* lipogenesis in the liver in association with alcohol consumption, leading to steatosis. Nonetheless, it remains to be determined whether ATF4-triggered amino acid synthesis and transport also contribute to the onset of steatosis in ALD.

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Secondary ER stress in ALD

ER stress can occur secondary to primary hepatic pathological stress. Mouse hepatocyte-specific knockout of diacylglycerol O-acyltransferase 1 (*DGAT1*), a rate-limiting enzyme of triglyceride synthesis, worsened steatosis and hepatocellular injury in ALD by promoting FFA build-up in the liver, thus triggering ER stress in concert with down-regulation of lysosomal associated membrane protein 2 (LAMP2) levels and defective autophagy. Mechanistically, FFA-induced ER stress activated the ATF4 branch to mediate LAMP2 down-regulation and subsequent inhibition of LAMP2-dependent autophagic flux. Moreover, lowering liver FFAs by peroxisome proliferator activated receptor α activation reversed ER stress, replenished LAMP2, and reactivated autophagy.[49] This finding suggests that inhibitory modulation of secondary ER stress (e.g., ATF4 or its upstream signals) may constitute a potential strategy for the treatment of hepatocellular injury and steatosis in ALD.

Activation of innate immune system is an essential component of ALD. Ethanol-induced secondary ER stress activated the STING1–interferon regulatory factor 3 (IRF3) signaling cascade. As a result, activated IRF3 interacted with and activated proapoptotic factor BCL2 associated X, apoptosis regulator (BAX), leading to hepatocyte apoptosis and ALD. *STING1* deficiency caused IRF3 inactivation, and therefore inhibition of hepatocyte apoptosis. Of note, these studies noted that IRF3-mediated pathogenic action did not rely on the presence of type I interferons or inflammation.[50] Taken together, the current literature denotes that ER stress occurs constitutively in or secondary to the state of ALD, leading to maladaptive UPR activation, thus promoting disease progression. In this regard, inhibition targeting of UPR components appears to be a proper therapeutic approach for the treatment of ALD.

ER STRESS IN CHRONIC HBV AND HCV

ER stress in HBV

Viral replication usurps host's cellular protein synthesis machinery. In this regard, HBV and HCV infection is associated with many components of ER stress signaling. He et al. revealed that level of B56γ subunit of protein phosphatase 2 catalytic subunit α (a major cellular serine/threonine phosphatase) was positively correlated with HBV x protein (HBx) levels in HBx-transgenic mice, hepatic cells expressing HBx *in vitro,* and human hepatocytes introduced into humanized chimeric mice.[51]. Mechanistically, HBx expression in hepatocytes induced ER stress, which in turn activated cAMP responsive element binding protein 3 like 3 (CREB3L3) signaling, leading to activation of Jun proto-oncogene, AP-1 transcription factor subunit (JUN) and its nuclear translocation, to transactivate gene encoding B56γ subunit. As a result, B56γ induced dephosphorylation of tumor protein p53 (TP53), and consequently CDKN1A activation, which triggered cell cycle arrest at the G1 phase and hepatocyte apoptosis.[51] Therefore, HBx-induced ER stress activates the CREB3L3-JUN-TP53-CDKN1A axis, which triggers cell cycle arrest and cell death, indicating that targeting ER stress could mitigate HBV-induced liver injury.

During HBV infection, several HBV envelope proteins are up-regulated in the ER. These envelope proteins include MHBs^t (truncated middle S protein) and LHBs (large S protein), which regulate gene expression of host hepatocytes, contributing to liver injury. Li et al. demonstrated that MHBs^t expression up-regulated IL-6 through activation of the mitogen-activated protein kinase 14 (MAPK14) and NF-κB pathways. Moreover, they showed that MHBs^t accumulation in the ER activated ER stress, which was perceived to be the underlying mechanism of activation for MAPK14 and NF-κB signaling.[52] Therefore, MHBs^t triggers ER stress–induced MAPK14 and NF-κB activation, which mediates IL-6 production and liver disease progression. Hence, suppressing ER stress and MAPK14 and NF-κB activation may diminish liver damage following HBV infection. Overall, these observations suggest that constitutive ER stress inflicts maladaptive effects and promotes HBV infection. Hence, inhibiting ER stress and maladaptive UPR may ameliorate HBV pathology.

ER stress in HCV

HCV is known to induce ER stress and up-regulate ER stress–associated genes. In line with this, it was reported that expression and replication of HCV proteins in the human liver Huh7 cell line, which carries complete HCV replicon, triggered ER stress and up-regulation of CHOP, resulting in apoptotic cell death. Further analysis revealed that ER stress–induced ATF4 and ATF6α components of UPR were responsible for up-regulation and activation of *DDIT3*/CHOP. Moreover, treating HCV replicon cells with H_2O_2 further increased *CHOP* up-regulation, suggesting that oxidative stress and ER stress can lead to *CHOP* up-regulation and cell death in HCV replicon cells. Furthermore, using small interfering RNA to suppress the *DDIT3* gene reversed cell death under oxidative and ER stress.[53] Hence, inhibitory targeting of ER stress and oxidative stress may prevent HCV-induced liver injury.

Asselah et al. also revealed features of ER stress and activation of all three UPR branches (IRE1α, ATF6α, and PERK) as well as up-regulation of inflammatory and apoptotic genes in infected hepatocytes from patients. Moreover, these investigators

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observed that ER-stressed hepatocytes formed clusters scattered across hepatic parenchyma. In addition, HCV managed to suppress UPR-responsive genes from propagating ER stress among hepatocytes via unknown mechanisms.[54] This study further pinpoints the potential of ER stress inhibition and activation of UPR-responsive genes in the management of HCV-induced liver damage.

Altogether, current available evidence suggests that ER stress induction under hepatitis B virus (HBV) and HCV infection is relatively severe, thus evoking persistent activation of UPR, resulting in the progression of hepatitis disease pathology. Hence, inhibition targeting of ER stress and the UPR branches may be a sensible approach in the management/treatment of HBV and HCV. However, generally, apoptosis is not a frequent feature of HBV or HCV infection, as both viruses usurp ER machinery to replicate. Therefore, it is very difficult to conceptualize these limited studies or learn the role of ER stress in HBV or HCV.

ER STRESS AND LIVER CANCER: HCC

Implications of the UPR in hepatocarcinogenesis

HCC is the most prevalent primary liver malignancy. ER stress and UPR activation occur in multiple malignancies including HCC. It is well-known that HBV potentiates HCC and serves as the primary cause of HCC globally. Recent data also suggest that HCC can result from NASH before onset of cirrhosis.[55] Shuda et al. assessed the expression of ATF6α, BiP, and XBP1 in HCC tissue samples and observed augmentation of *ATF6α* and *HSPA5* mRNAs, accumulation of BiP in the cytoplasm, increased nuclear localization of ATF6p50, and XBP1 mRNA splicing, in association with more severe histological scores.[56] Hence, ER stress–activated UPR branches such as ATF6α and IRE1α may play a role in hepatocarcinogenesis.[56,57]

In addition, mutation profiling in human HCC identified nonsynonymous mutations in numerous ATF6α target genes and a somatic mutation in a gene that prevents ATF6α degradation, thus promoting ATF6α accumulation and activation.[58] On the other hand, a single nucleotide polymorphism in *ATF6α* increased levels of *ATF6α* mRNA, ATF6α target genes, and susceptibility to HCC.[59] It is noteworthy that *ATF6α* loss-of-function mutations possess a mild phenotype in human, resulting in achromatopsia—a form of progressive retinal degeneration[60,61]—suggesting that short-term inhibition of *ATF6α* may be affordable to treat human NASH and HCC.

Moreover, IRE1α signaling plays a significant role in HCC onset, as hepatic-specific *IRE1* deficiency prevented HCC development in mice under diethylnitrosamine treatment.[62] *IRE1* deficiency was accompanied by signal transducer and TANGO1, transport and Golgi organization 1 (STAT3) activation, restrained hepatocyte proliferation, enhanced hepatocyte apoptosis, and attenuated levels of TNF-α and IL-6.[62] It is perceived that UPR activation is an adaptive mechanism in malignant hepatic cells to cope with ER stress under unfavorable environmental conditions and chemotherapeutic drugs. However, severe/constitutive ER stress may induce cell death in HCC cells, thus exhibiting promises in the prevention of HCC progression. Moreover, pharmacological inhibition of IRE1α endoribonuclease activity reduced tumor burden in mice with fibrotic HCC.[63] Treatment with the IRE1α inhibitor 4μ8c blocked stellate cell activation, restrained proliferation and migration of tumor cells in 2-dimensional and 3-dimensional *in vitro* co-cultures, possible due to reduced levels of intracellular reactive oxygen species. Hence, IRE1α may play a role in the crosstalk between HSCs and tumor cells in liver cancers and possess therapeutic promises as a pharmacological target.

Mild ER stress and adaptive UPR in HCC

Examining zinc finger protein 263 (ZNF263; a transcription factor) in the face of ER stress–mediated drug resistance in HCC cell lines and patients with HCC revealed that *ZNF263* was significantly up-regulated. In addition, level of *ZNF263* was found to correlate with ER stress, clinical stage, and shorter survival of patients with HCC. Mechanistically, ZNF263 induced ER stress, and subsequently autophagy, which conferred chemoresistance to HCC cells. Thus, *ZNF263* knockdown using RNA interference diminished proliferation, reduced chemoresistance, and enhanced apoptosis in HCC.[64] This study suggests that ZNF263-induced ER stress provokes adaptive autophagy, which reduces the sensitivity of HCC cells to chemotherapeutic drugs. Hence, abrogating autophagy may boost the anticancer effect of chemical drugs.

Liu et al. reported up-regulation of ER stress markers including BiP/*HSPA5*, ATF6α, PERK/*EIF2AK3*, and IRE1α/*ERN1* in HCC tissues, which was negatively correlated with the overall patient survival, recruitment of cluster of differentiation (CD) 68^+ macrophages, and CD274 expression in HCC tissues. HCC cells exposed to tunicamycin (an ER stress inducer) were found to release abundant EV-containing microRNA *(MIR)-23a-3p*, and MIR-23a-3p may be responsible for the up-regulation of *CD274* in macrophages both *in vivo* and *in vitro*. Mechanistically, *MIR-23a-3p* regulated *CD274* by inhibiting phosphatase and tensin homolog (*PTEN*) expression, and therefore enhanced AKT serine/threonine kinase 1 (AKT1) phosphorylation (activation), leading to up-regulation of *CD274*. Moreover,

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coculturing T cells with EV-treated macrophages induced T cell apoptosis and reduced $CD8^+$ T cell levels.[65] Hence, this study suggests that ER-stressed HCC cells release EV to confer T cell–immunosuppressive properties to macrophages.

Severe/constitutive ER stress and maladaptive UPR in HCC

Severe/constitutive ER stress and unchecked UPR may be useful in the treatment of HCC. For example, Lee et al. applied combination of TNF superfamily member 10 (TNFSF10; a cytokine that induces apoptosis) and nonsteroidal anti-inflammatory drugs (NSAIDs) on TNFSF10-resistant/*CD44*-expressing HCC cells. They discovered that the NSAID celecoxib and its derivative 2,5-dimethyl celecoxib reversed TNFSF10 resistance in HCC cells. Mechanistically, celecoxib dose-dependently induced ER stress, ATF4 and *CHOP* expression, protein kinase AMP-activated catalytic subunit α2 (PRKAA2 or AMPK) activation, and inhibition of AKT1–mechanistic target of rapamycin kinase (MTORC1) pathway, leading to facilitated autophagy, as indicated by increased microtubule associated protein 1 light chain 3β (MAP1LC3B) levels and decreased p62 levels.[66] Altogether, this finding suggests that combination of NSAID and TNFSF10 improves the clinical efficacy of TNFSF10-based HCC therapy likely through induction of profound ER stress and unchecked autophagy.

To investigate the role of ER stress in obesity-induced liver tumorigenesis, Nakagawa et al. used HFD-fed wild-type and *MUP*–plasminogen activator, urokinase (*PLAU*) mice. In *MUP-PLAU* transgenic model, hepatocyte-specific overexpression of *PLAU* causes hepatocyte ER stress at 6 weeks of age that is attenuated by 10 weeks due to extinction of *PLAU* expression. When fed an HFD starting at 10 weeks, *MUP-PLAU* mice developed symptoms of human NASH and HCC by 9 months. Thus, transient ER stress is sufficient to establish an environment conducive to NASH and HCC development after subsequent HFD feeding. Indeed, both HFD-fed wild-type and *MUP-PLAU* mice were insulin-resistant, although *MUP-PLAU* mice displayed more pronounced liver injury, lipogenesis, and immune infiltration, resulting in NASH and steatohepatitis-driven HCC. Mechanistically, hepatocyte ER stress in *MUP-PLAU* mouse livers stimulated the recruitment of inflammatory macrophages to produce TNF and contribute to the pathogenesis of NASH and HCC.[55] These findings consolidate the notion that ER stress is embedded in a molecular cascade leading to hepatic carcinogenesis.

In summary, the role of ER stress and the UPR is a double-edged sword in HCC, as these malignant cells hijack adaptive UPR to suppress mild ER stress and maintain cell growth and proliferation. On the other side of the coin, induction of severe ER stress and constitutive UPR serves as an effective measure to eliminate carcinomatous cells through UPR-dependent cell death.

ER STRESS AND LIVER ISCHEMIA/REPERFUSION INJURY

ATF6α in liver ischemia/reperfusion injury

The contribution of ER stress to ischemia-associated deregulation of innate immunity is largely elusive. Rao et al. observed that warm ischemia evoked ER stress and UPR in mice, particularly ATF6α signaling in Kupffer cells (KCs), thus modulating their response to toll-like receptor (TLR) agonists. As a result, ischemic and ER-stressed KCs reduced the production of anti-inflammatory cytokines but enhanced that of pro-inflammatory cytokines. Suppression of ER stress by means of the chemical chaperon 4–phenylboronic acid (PBA) or silencing ATF6α by small interfering RNAs curbed pro-inflammatory cytokine production and consequently dampened the local activation of immune cells.[67] This study suggests that inhibiting ER stress may be beneficial for inflammatory complications of hepatic ischemia.

IRE1-α in liver ischemia/reperfusion injury

Ischemic preconditioning confers partial protection from ischemia/reperfusion (I/R) injury. In an *in vivo* model of ER stress preconditioning, Liu et al. injected rats with tunicamycin before liver I/R challenge.[68] Meanwhile, these researchers treated L02 and HepG2 cells with tunicamycin and thapsigargin. Liver I/R injury was apparently mitigated by ER stress induction and subsequent activation of IRE1α and BiP signaling. Of note, these authors observed that IRE1α interacted with receptor for activated C kinase 1 (RACK1), leading to the activation of IRE1-RACK1-PRKAA2 and IRE1-RACK1–BCL2 apoptosis regulator (BCL2) pathways, culminating in apoptosis inhibition and autophagy induction.[68] This study suggests that ER stress preconditioning can alleviate liver I/R damage through activation of the IRE1-RACK1 axis.

Secondary ER stress in liver I/R injury

Lu et al. investigated the impact of ER stress on IL-23A production following I/R liver injury *in vivo* and *in vitro*. These authors revealed that ischemia up-regulated *IL23A* and *IL12B* in liver nonparenchymal cells, leading to an immune response against I/R injury and

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progression of hepatocellular inflammation and injury. It is believed that ER stress induction, autophagy inhibition, and TLR4 activation serve as the main underlying mechanism of *IL23A* and *IL12B* up-regulation. Therefore, inhibiting TLR4 and alleviating ER stress using rapamycin and 4-PBA, respectively, led to inhibition of IL23A production and liver protection from I/R injury.[69] This study denotes a synergistic effect among ER stress induction, autophagy inhibition, and TLR4 activation in I/R-induced liver injury. In conclusion, the current literature uncaps both preventive and promoting role of ER stress and UPR in liver I/R injury, depending on the extent and severity of ER stress and UPR activation.

ER STRESS AND LIVER FIBROSIS AND CIRRHOSIS

IRE1α in liver fibrosis

Fibrogenic signals trigger transcription of procollagen I, which then enters the ER and passes through the ER-Golgi secretory compartment to be released into the extracellular matrix. Maiers et al. observed that perturbation of ER export of procollagen I induced ER stress and UPR activation, leading to apoptosis in HSCs.[70] They also revealed that HSC-specific depletion of TANGO1 (a protein that participates in collagen I secretion) suppressed collagen I secretion, resulting in ER retention of procollagen I, ER stress, UPR induction, and apoptosis, thereby alleviating hepatic fibrosis in murine and human tissue samples.[70] Further analysis showed that the IRE1α-XBP1s axis could induce TANGO1 up-regulation following TGF-β treatment.[70] This study suggests a key role for TANGO1 in hepatic fibrosis by facilitating collagen I secretion. UPR activation induces TANGO1 up-regulation, thus promoting hepatic fibrosis. On the contrary, TANGO1 deficiency triggers UPR-mediated cell death, thereby slowing down fibrogenesis.

PERK in liver fibrosis

HSCs play a major role in the development of liver fibrosis, a pathological state due to the accumulation of extracellular collagen fibers. Exploration of ER stress in HSCs obtained from patients with HCV infection/fibrosis or mice showed that ER stress evoked activation of HSCs, up-regulation of fibrogenic genes, as well as enhanced levels of the pro-fibrotic signaling molecule SMAD family member 2 (SMAD2). Targeted delivery of an *HSPA5* lentivirus to murine HSCs attenuated hepatic fiber accumulation. Also, *SMAD2* knockdown using small interfering RNA attenuated ER stress–induced HSCs activation. Mechanistically, ER stress–induced PERK caused phosphorylation of heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) at Thr51, targeting it for proteasomal degradation. As a result of HNRNPA1 degradation, *MIR-18A* (a suppressor of SMAD2 expression) declines, thus leading to enhanced expression of *SMAD2* in murine HSCs. On the contrary, induction of *HNRNPA1* expression inhibited liver fibrosis.[71] In summary, this study suggests that ER stress in HSCs switches on the PERK-HNRNPA1-*MIR-18A*-SMAD2 signaling to promote liver fibrosis, offering a new druggable target for liver fibrosis.

Moreover, examination of ER stress in portal myofibroblasts (PMF) using a rat model of bile duct ligation–induced liver fibrosis revealed that PMF up-regulated myofibroblastic markers (*ACTA2* and collagen type I α1 chain [*COL1A1*]) and became more proangiogenic, yet dampened their lower migratory and proliferative capabilities. Moreover, fibrotic rat PMF displayed ER stress, as indicated by activation of PERK and its downstream proteins including CHOP, GADD34, and TRB3. The PERK inhibitor GSK2656157 suppressed ER stress, thus attenuating the proangiogenic properties of fibrotic rat PMF and restoring their migratory and proliferative capacity.[72] Therefore, inhibitory targeting of the ER stress kinase PERK may alleviate liver fibrosis.

Secondary ER stress in liver fibrosis and cirrhosis

Inflammation plays a significant role in the onset and progression of liver fibrosis. It is well known that IRF3, which is activated by the pro-inflammatory proteins TLR4 and STING1, may trigger hepatocyte apoptosis and favors type I interferon responses. Chronic administration of the liver fibrosis–inducing toxin carbon tetrachloride (CCl_4) resulted in the induction of secondary ER stress, IRF3, and type I interferon activation, apoptosis, liver damage, and fibrosis. However, acute/chronic administration of CCl_4 to the *IRF3*-deficient or *STING1*-deficient mice failed to induce apoptosis and fibrosis in hepatocytes, suggesting an obligatory role for IRF3 and STING in CCl_4-induced liver fibrosis. Conversely, mice deficient in type I interferon receptors or TLR4 adaptors (toll like receptor adaptor molecule 1 [*TICAM1*] and translocation associated membrane protein 1 [*TRAM1*]) developed hepatocyte apoptosis and liver fibrosis.[73] These findings suggested that ER stress–induced STING1-IRF3 signaling cascade triggers up-regulation of type I interferons, resulting in hepatocyte apoptosis and aggravation of liver fibrosis independent of TLR4 signaling.

Zhu et al. characterized the effects of salvianolic acid A (SalA, a traditional antioxidant) on liver fibrosis and SIRT1 signaling in an *in vitro* model of fibrosis (LX2 human hepatic stellate cell line exposed to platelet-

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TABLE 1 Bioactive alleviators for hepatic ER stress and UPR in mammalian cells

Compound	Full name/source	Mechanisms of action	Refs
4-AAQB	4-acetylantroquinonol B (natural ubiquinone derivative extracted from mycelia of *Antrodia cinnamomea*)	Ameliorates ER stress and inflammation in J774A.1 and RAW264.7 cellular model of NAFLD and C57BL/6J mice fed choline/methionine-deficient diet	[87]
Berberine	Natural compound found in several herbal plants	Reverses ER stress and ER stress–induced lipogenesis via ATF6α /SREBF1 axis in mice and hepatocyte cell lines, confers resistance to steatosis, and diminishes liver fibrosis and lipid peroxides	[88]
Betaine	Nutrient	Reduces serum homocysteine levels, dampens severe ER stress and UPR in the liver in alcohol-fed mice	[89]
Bicyclol	Chemical compound	Ameliorates mouse fatty liver by attenuating ER stress–triggered apoptosis and down-regulation of *DDIT3*, *HSPA5*, *ERN1*, and *ATF6α*	[90]
Curcumin	Natural compound derived from *Curcuma Longa*	Reduces liver ER stress and ER stress markers (BiP, PERK, IRE1, TRAF2, TNF, IL1B, MAPK14, MAP3K5, and CEBPB) in diabetic rat liver, suppresses ER stress–mediated apoptosis, and boosts liver histopathological and morphological changes and function	[91]
Empagliflozin	Medication for type 2 diabetes treatment	Reduces fasting glucose, total TG and cholesterol levels, levels of inflammatory molecules and lipogenic enzymes, and ER stress proteins (BiP, IRE1, XBP1, eIF2α, ATF6α, ATF4, CHOP, SQSTM1, and HSP90B1), induces adaptive autophagy, and inhibits CASP8 cleavage and apoptosis to relieve NAFLD in HFD-fed mice	[92]
Fenofibrate	Medication to reduce blood TG and cholesterol	Ameliorates NAFLD in high-cholesterol diet–fed C57BL/6 mice via suppressing ER stress, inflammation, apoptosis, down-regulating *ERN1* and *XBP1*, and reducing MAPK8 phosphorylation	[93]
Ginsenoside Mc1	Compound found in ginseng	Protects from ER stress–induced apoptosis, lipogenesis, and insulin resistance in palmitate-treated HepG2 cells and obese mice	[94]
Homocysteine	An amino acid	Mitigates ER stress and replenishes liver S-adenosylmethionine, resulting in alleviation of steatohepatitis in a mouse model of steatohepatitis and cultured hepatocytes. Reduces TNF production from liver macrophages in NASH	[95]
Kaempferol	Antioxidation and anti-inflammatory flavonoid	Reduces lethality, increases survival time, and alleviates liver injury via inhibition of ER stress–induced apoptosis, down-regulation of *DDIT3*, and up-regulation of *HSPA5* in mice with acute liver failure and *in vitro* model	[96]
Lactobacillus rhamnosus GG	Friendly bacteria in intestines	Down-regulates ER stress and ROS and liver *HSPA5* and *DDIT3* expression, and normalizes autophagy in acute alcohol–triggered liver damage in C57BL/6 mice	[97]
Liraglutide	Analog of glucagon-like peptide-1	Alleviates ER stress and attenuates chemerin expression in rat livers in HFD-induced insulin resistance	[98]
Matrine	Alkaloid obtained from *Sophora flavescens*	Reverses ER stress, repairs mitochondrial dysfunction, shrinks lipid accumulation and Ca^{2+} overload by inhibiting ATP2A2, and reduces lipid peroxides and inflammation in the liver of C57BL/6J mice under HFD	[99]
Melatonin	Pineal gland released hormone	Suppresses severe UPR activation and ER stress–induced apoptosis, and attenuates expression of *DDIT3*, *HSPA5*, *HSP90B1*, *MAPK8*, and *CASP12* in a rabbit model of fulminant hepatitis ATP2A2;	[100]

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TABLE 1. (*continued*)

Compound	Full name/source	Mechanisms of action	Refs
		disrupts tunicamycin-caused ER stress via down-regulation of *MIR-23a* in primary hepatocytes; and alleviates liver steatosis and inflammation	[101]
Metformin	Medication for type 2 diabetes treatment	Inhibits palmitate-caused ER stress and liver insulin resistance, and down-regulates *HSPA5*, *DDIT3*, *ATF6α*, *eIF2α*, and *XBP1* in HepG2 cells	[102]
Pioglitazone	Antidiabetic medication	Suppresses ER stress and insulin resistance in diabetic mouse liver	[103]
Quercetin	Natural flavonoid	Resolves ER stress, oxidative stress, and hepatotoxicity in rat livers exposed to lead, and reduces IRE1 and MAPK8 levels in rat livers	[104]
Rapamycin	Macrolide compound	Protects the liver from I/R injury via down-regulation of ER stress proteins, and inhibits maladaptive UPR in murine and *in vitro* models of I/R injury	[105]
Salvianolic acid B	Natural antioxidant	Suppresses ER stress and hyperactivation of ER stress molecules (CHOP, PERK, and IRE1), refines glucose tolerance, and improves insulin resistance in the liver of ob/ob mice	[106]
Schisandra chinensis methanol extract	Chinese herbal medicine	Suppresses ER stress, levels of lipogenic and inflammatory genes, and triglyceride accumulation, and alleviates NAFLD in HepG2 cells and obese mice under tunicamycin or palmitate treatment	[107]
Silymarin	Chemical compound	Reverses pathologies associated with NAFLD such as ER stress, lipid profile, AST, ALT, HSAP5, and XBP1 levels	[108]
Taurine	Amino sulfonic acid	Suppresses ER stress, oxidative stress, CASP3 activation, and apoptosis in H4IIE cells and primary hepatocytes in diet-induced NAFLD models; and counters liver injury, inflammation, lipid accumulation, plasma TG levels	[109]
Vitamin C	Vitamin abundantly found in foods	Ameliorates perfluorooctane sulfonate–triggered murine liver steatosis via suppression of maladaptive UPR and ER stress as demonstrated by down-regulation of *ATF6α*, *eIF2α*, *HSPA5*, and *XBP1*, and inhibition of hepatocellular inflammation	[110]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP2A2, ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2; CEBPB, CCAAT enhancer binding protein β; DDIT3, DNA damage inducible transcript 3; ERN1, endoplasmic reticulum to nucleus signaling 1; HFD, high-fat diet; HSP90B1, heat shock protein 90 β family member 1; MIR-23a, microRNA 23a; SQSTM1, sequestosome 1; SREBF1, sterol regulatory element binding transcription factor 1; TG, triglycerides; TRAF2, TNF receptor associated factor 2.

derived growth factor-BB homodimer) and *in vivo* (bile duct ligation) rat models. These researchers found that SalA treatment alleviated ER stress and liver fibrosis via activation of the SIRT1-HSF1 pathway *in vivo* and *in vitro*. Mechanistically, SIRT1 activation induced deacetylation and up-regulation of HSF1, which stimulated the heat shock response to facilitate proper folding of ER proteins, thus alleviating ER stress and liver fibrosis.[74]

ER stress upstream signaling molecules have been identified as druggable targets for intervention of liver fibrosis. In a rodent model of CCl_4-induced liver fibrosis, inhibition of epoxide hydrolase 2 (EPHX2; involved in lipid epoxides metabolism) using 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU) attenuated extracellular collagen deposition and down-regulated collagen type I α2 chain (COL1A2)/collagen type III α1 chain (COL3A1) by 50%. Moreover, CCl_4-induced murine liver fibrosis was accompanied by ER stress due to activation of all three UPR pathways (IRE1α, PERK, and ATF6α), which was alleviated by TPPU treatment.[75] Overall, these data suggest that induction of ER stress occurs downstream of EPHX2, which is a druggable target.

Angiotensin II (Ang-II) is a vasoactive molecule in the renin-angiotensin system and plays a key role in liver fibrosis. Mechanistically, Ang-II mediates inflammatory cytokine production, collagen synthesis, proliferation, and mitogenesis in activated HSCs, resulting in development of liver fibrosis.[76] Fang et al. treated human LX2 cells with Ang II either alone or in combination with mitogen-activated protein kinase kinase kinase 5 (MAP3K5) inhibition (using GS-4997) or its silencing (using small interfering RNA) and revealed that Ang II

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TABLE 2 Bioactive compounds that trigger ER stress–dependent apoptosis in liver cancer

Compound	Description	Mechanisms of action	Refs
Annona muricata L. ethanol extract	Plant that contains chemical agents for cancer treatment	Induces ER-stressed apoptosis via enhanced BiP, PERK, HSP90B1, DPYSL5, eIF2α, and CHOP in HepG2 cells	[111]
Bacitracin	Cyclic polypeptide antibiotic	Inhibits P4HB, inducing ER stress and apoptosis in HCC *in vivo*; and boosts anticancer effect of 3-bromopyruvate (inhibitor of HK2) by augmenting ER stress–regulated apoptosis	[112]
b-AP15	Selective inhibitor of USP14	Induces ER stress and UPR, blocks WNT1-NOTCH1 signaling, reduces cell viability, fosters apoptosis, and perturbs cell cycle in HCC cells	[113]
Celastrol	Extracted from the root of *Tripterygium regelii* and *Tripterygium wilfordii*	Induces ER stress and activates EIF2A-ATF4 axis, leading to activation of PMAIP1 (pro-apoptotic factor) and apoptosis in combination with ABT-737 drug in HCC cells	[114]
Dehydrocostuslactone	Natural sesquiterpene lactone derived from medicinal plants	Blocks HepG2 and PLC/PRF/5 cell proliferation and limits tumor volume by triggering ER stress–induced apoptosis via up-regulation of *EIF2AK3*, *ERN1*, and *DDIT3*, and increased splicing of XBP1 and CASP4 activation	[115]
3,3-Diindolylmethane	Obtained from the digestion of indole-3-carbinol that exists in cruciferous vegetables	Remarkably restrained HCC cell growth, migration, invasion, and proliferation via induction of ER stress–triggered apoptosis in human HCC Huh7 and Hep3B cells	[116]
Ginsenoside compound K	20-*O*-β-d-glucopyranosyl-20(*S*)-protopanaxadiol	Induces apoptosis via up-regulation of UPR branches and reduces STAT3 levels, and blocks colony formation and growth of HCC in human HepG2 and SMMC-7721 cells and human HCC xenografts	[117]
Isovitexin	Glycosylflavonoid derived from hulls in rice *Oryza sativa*	Suppresses hepatic cancer cell growth *in vivo* by inducing apoptosis through *BAX* up-regulation, enhanced CASP3 cleavage, increased PARP1 and mitochondrial cytochrome c release, induction of prolonged autophagy, and severe ER stress	[118]
Meloxicam	Anti-inflammatory drug and selective inhibitor of PTGS2	In combination with sorafenib, induces ER stress–mediated apoptosis in human HCC SMMC-7721 cells and *in vivo* models	[119]
N-acetylcysteine	Antioxidant	Abates HCC progression via suppressing ER stress and oxidative stress, UPR, and inflammation in *TLR2*-knockout mice, and reduces SQSTM1 aggregation in liver	[120]
4-*O*-carboxymethyl ascochlorin	Synthetic ascochlorin derivative	Triggers ER stress and enhances *HSPA5* and *DDIT3* expression and autophagy protein levels (BECN1, ATG5, and MAP1LC3A), resulting in apoptosis and autophagy-dependent cell death in human HCC HepG2 cells	[121]
Piperlongumine	Alkaloid extracted from long pepper fruit	Induces lethal ER stress in HCC *in vivo* via interacting and inhibiting TXNRD1, resulting in intracellular ROS production	[122]
Safranal	Natural compound extracted from saffron	Induces ER stress–caused apoptosis, caspases activation, and DNA-strand breakage in HCC HepG2 cells	[123]
Scutebarbatine A	Alkaloid found in *Scutellaria barbata* D. Don	Inhibits HCC cells growth, and induces cell cycle arrest and apoptosis via excessive ER stress and UPR induction (up-regulates *DDIT3*, *ATF6α*, and *EIF2AK3*)	[124]
Sorafenib	Anticancer kinase inhibitor drug	Induces ER stress, leading to apoptosis in human HCC cells, and up-regulates *ERN1*; its combination with chloroquine (autophagy blocker) promotes ER stress–dependent cell death	[125]

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TABLE 2. (*continued*)

Compound	Description	Mechanisms of action	Refs
SNX-2112	Inhibitor of HSP90AB1	Induces apoptosis via ER stress induction, inhibition of BiP, and all UPR branches in SK-Hep1, Huh7, and HepG2 and murine xenograft models	[126]
Sodium demethylcantharidate	Cantharidin derivative	Blocks proliferation of Bel-7402 and SMMC-7721 HCC cells and human HCC xenograft models in a dose-dependent and time-dependent pattern via induction of severe ER stress, leading to apoptosis	[127]
V8	Chemical compound	Induces ER stress–mediated apoptosis via hyperactivation of BiP, PERK, eIF2α, ATF4, and CHOP, and thus ceases growth of HCC HepG2 cells in a dose-dependent pattern	[128]

Abbreviations: ATG5, autophagy-related 5; BAX, BCL2 associated X, apoptosis regulator; BECN1, beclin 1; DPYSL5, dihydropyrimidinase like 5; EIF2AK3, eukaryotic translation initiation factor 2 alpha kinase 3; HK2, hexokinase 2; HSP90AB1, heat shock protein 90 α family class B member 1; MAP1LC3A, microtubule associated protein 1 light chain 3 α; NOTCH1, notch receptor 1; P4HB, prolyl 4-hydroxylase subunit β; PARP1, poly[ADP-ribose] polymerase 1; PTGS2, prostaglandin-endoperoxide synthase 2; STAT3, signal transducer and TANGO1, transport and Golgi organization 1; TLR2, toll-like receptor 2; TXNRD1, thioredoxin reductase 1; USP14, ubiquitin specific peptidase 14; WNT1, Wnt family member 1.

overtly up-regulated proinflammatory cytokines (*IL1B*, *IL18*, and *TNF*), extracellular matrix proteins (*ACTA2*, *COL1A1*, and *COL3A1*), and ER stress markers (*HSPA5*, *EIF2AK3*, *DDIT3*, and *MAP3K5*). However, these effects were abolished by GS-4997 treatment or *MAP3K5* silencing. In addition, ER stress–induced MAP3K5 signaling induced EV release, which activated LX2 cells to promote liver fibrosis. Inhibition of EV uptake curtailed activation of LX2 cells and alleviated liver fibrosis *in vitro*.[77] This study suggests that Ang

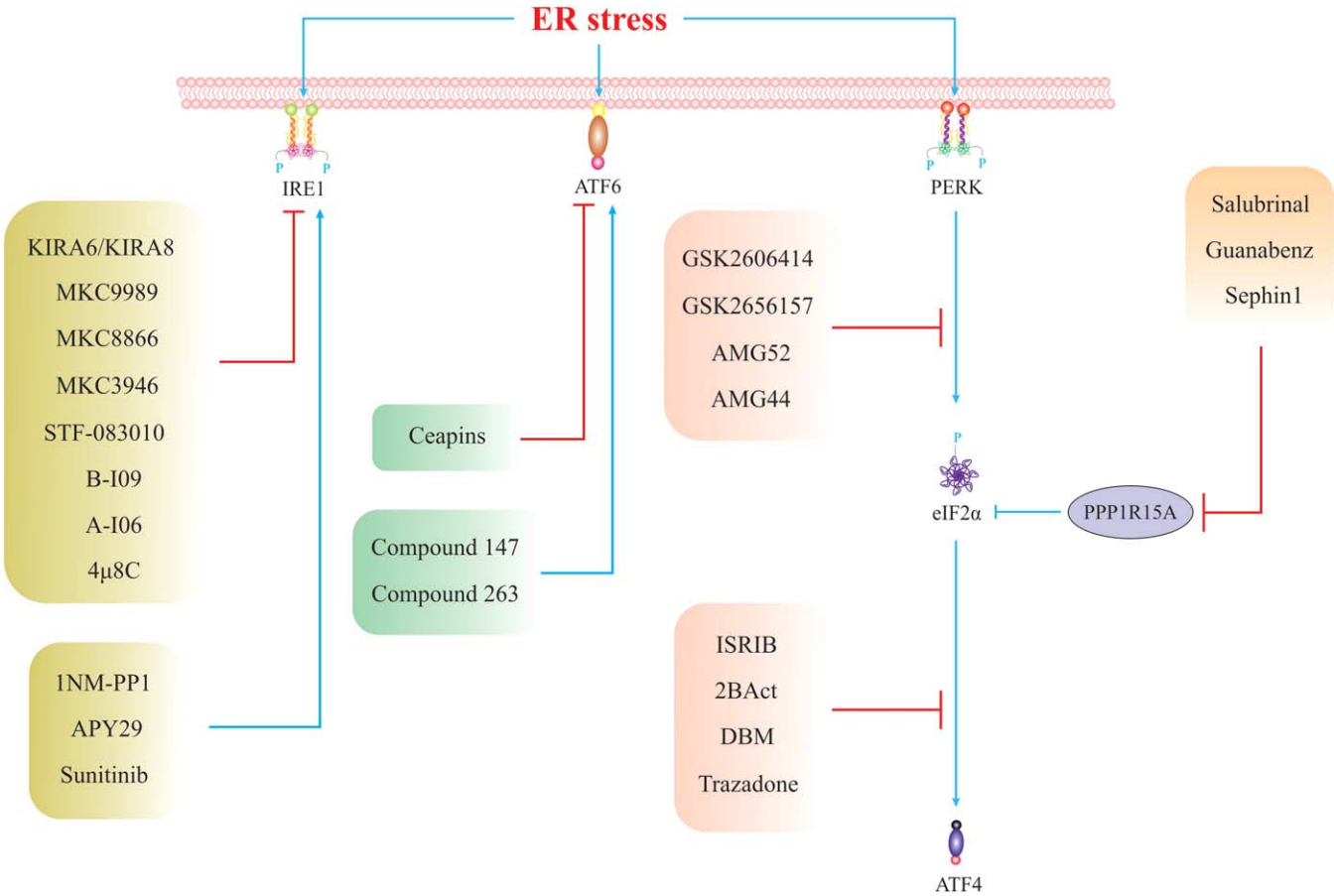

FIGURE 3 Small molecules targeting UPR branches. List of small chemicals for specific targeting of UPR components.[129,130] Given that most of these compounds have not been examined in the context of liver diseases, future studies are warranted to examine these compounds in the context of liver disease in both preclinical and clinical studies.

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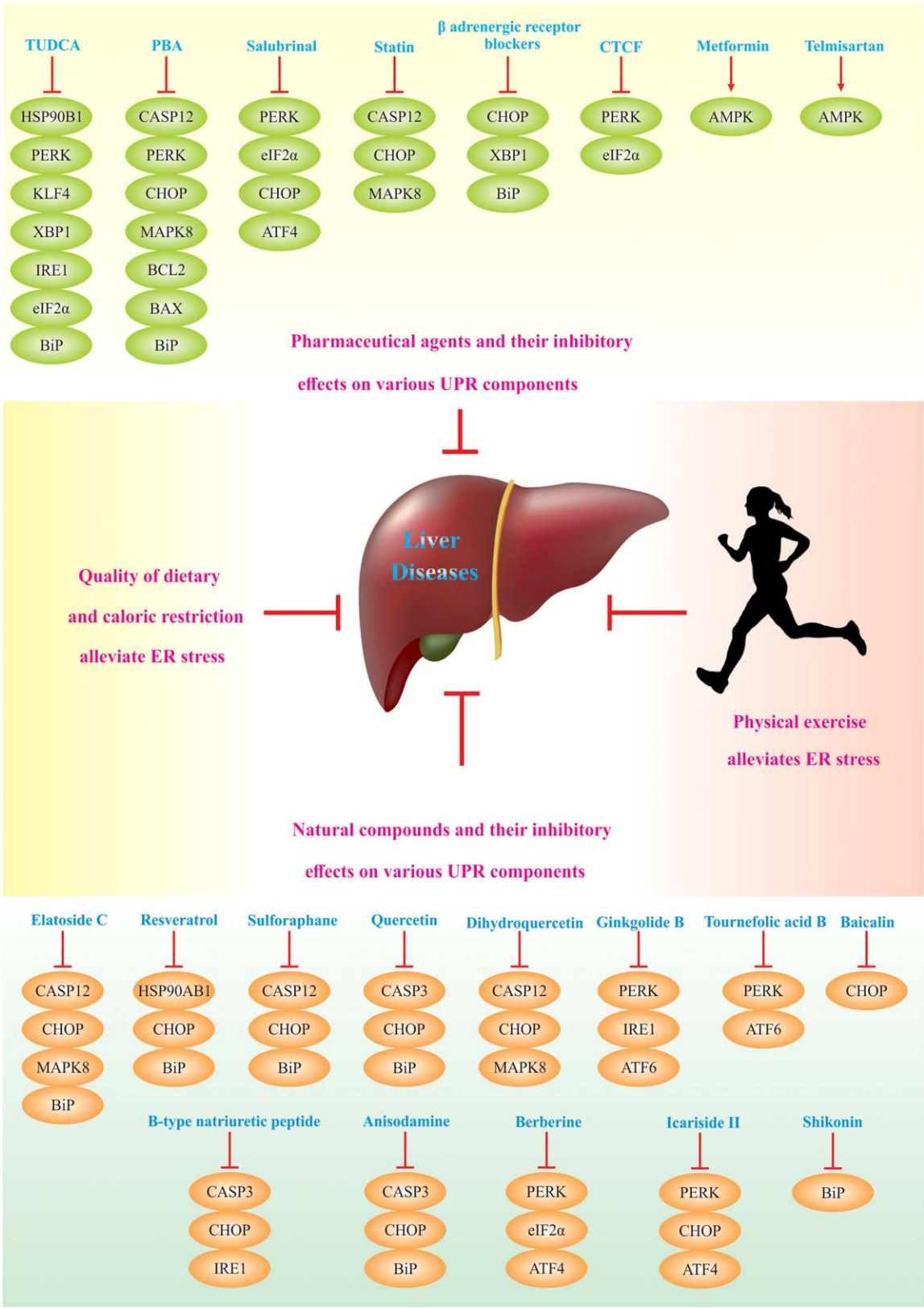

FIGURE 4 Targeting ER stress in liver diseases. Overall, pharmaceutical and natural agents, physical exercise, and caloric restriction diminish ER stress, and therefore alleviate nonmalignant liver diseases. Pharmaceutical agents suppress UPR components or activate protein kinase AMP-activated catalytic subunit α2 (AMPK). Similarly, natural compounds being found abundantly in vegetables, fruits, herbs, spices, and beans target UPR components. Caloric restriction and physical exercise confer similar effects on ER stress alleviation and liver diseases management. BCL2, BCL2 apoptosis regulator; BiP, binding immunoglobulin protein; CTCF, cellular CCCTC-binding factor; PBA, phenylboronic acid; TUDCA, tauroursodeoxycholic acid.

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II–induced liver fibrosis involves induction of ER stress, which triggers pathogenic EV release via MAP3K5 signaling.

Finally, intraperitoneal administration of thioacetamide to Sprague-Dawley rats induces liver cirrhosis. In this model, Su et al. demonstrated that celecoxib (an inhibitor of prostaglandin-endoperoxide synthase 2 for prostaglandin biosynthesis) significantly attenuated serum levels of alanine aminotransferase and aspartate aminotransferase (markers of liver injury), alleviated ER stress and ER stress markers (BiP, PERK, ATF6α, and IRE1), and reduced apoptotic markers (CHOP, CASP12, and CASP3), leading to mitigation of liver fibrosis and cirrhosis.[78] This study suggests that blocking ER stress–induced apoptosis using celecoxib can effectively prevent cirrhosis, calling for the demand for specific clinical trials.

Taken together, these data conclude that liver fibrosis and cirrhosis are accompanied by severe ER stress, leading to constitutive activation of the UPR branches such as PERK and IRE1α, thus promoting the disease pathology. Hence, therapeutic suppression of the UPR pathways may ameliorate liver fibrosis and cirrhosis.

THERAPEUTIC MANIPULATION OF ER STRESS FOR LIVER DISEASE TREATMENT AND MANAGEMENT

Natural and pharmaceutical compounds for ER stress manipulation

Given that prolonged ER stress contributes to the pathogenesis of multiple liver diseases, it is important to develop therapeutic strategies to curtail maladaptive UPR. Table 1 lists several natural and pharmaceutical compounds with the potential to suppress maladaptive UPR or alleviate ER stress. Table 2 lists anticancer agents that induce ER stress–dependent cell death in HCC or other malignant tumors in the liver. Figure 3 summarizes current knowledge on small therapeutic molecules that specifically elicit or inhibit one of the three UPR branches.

Chemical chaperones: tauroursodeoxycholic acid and 4-PBA

Chemical chaperones such as tauroursodeoxycholic acid (TUDCA) and 4-PBA alleviate ER stress by increasing protein-folding capacity. Such molecules might be useful for the management of liver diseases associated with ER stress. For example, TUDCA alleviates the cytotoxicity of polyhexamethyleneguanidine, an antimicrobial agent, against HepG2 cells. Moreover, TUDCA ameliorated ER stress–induced apoptosis and mitochondrial depolarization.[79] TUDCA boosts multiorgan insulin sensitivity by enhancing protein folding and ameliorating ER stress. In a clinical trial enrolling 20 obese individuals, TUDCA improved insulin sensitivity of the liver and muscle.[80] Moreover, in an HFD-induced mouse model of NAFLD, TUDCA was found to suppress ER-associated gut inflammation, insulin resistance, obesity, and liver steatosis.[81] Similarly, intraperitoneal injection of 4-PBA into C57BL/6 mice with hepatic I/R injury lowered expression of *DDIT3* and eIF2α phosphorylation as well as inhibited ER stress–initiated apoptosis coupled with CASP12 activation. 4-PBA also remarkably attenuated signs of systemic and hepatic inflammation, such as plasma TNF levels and liver MPO, respectively.[82] 4-PBA also potently reduces hepatotoxicity of industrial toxicant perfluorooctanoic acid (PFOA). 4-PBA alleviated ER stress and blocked ER stress–induced hyperactivation of autophagy in mouse livers and HepG2 cells exposed to PFOA. 4-PBA also ameliorated other hepatotoxic PFOA-induced effects such as impairment of proteolytic activity, lipid accumulation, and cell cycle arrest.[83] Altogether, the current state of the literature suggests that chemical chaperones could be useful for the treatment of ER stress–associated liver diseases (Figure 4).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Mild ER stress activates adaptive UPR, while severe ER stress triggers maladaptive UPR, leading to cell death. Accumulating clinical and experimental evidence has consolidated the involvement of maladaptive UPR in the pathogenesis of liver diseases. Although maladaptive UPR promotes metabolic diseases, drug toxicity, and viral infections, it can be used as a tool to eliminate cancer cells that emerge in liver malignancies. Therefore, inhibitory targeting of maladaptive UPR could be pursued in nonmalignant liver diseases, while inducing severe ER stress could be implemented in the context of liver cancers. In this context, multiple studies have identified and characterized natural and pharmaceutical compounds that induce severe ER stress or, on the contrary, alleviate ER stress in the liver. Chemical chaperones, PE, and CR have a high potential to relieve ER stress and maladaptive UPR in liver diseases. Moreover, it is noteworthy that several intrinsic hepatic hormones and growth factors including FGFs display a robust decline in various hepatic injury such as NAFLD and NASH in association with disturbed ER homeostasis.[84–86] Although FGFs exhibited promises as novel therapeutic options of hepatic and other metabolic anomalies, possible involvement of ER stress and UPR remains unclear. One burning issue for future research is the identification of novel ER stress modulators that specifically intervene maladaptive UPR in the liver, without affecting adaptive UPR in other organs, or on the contrary, specifically elicit lethal UPR in liver cancer without triggering unwarranted ER stress responses in normal tissues. Moreover, there is a

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notable lack of studies on *IRE1* or *ATF6* knockout mouse models in liver disease, thus mandating future research on such models. In addition, more effort should be made with regard to the impact of ATF6α or IRE1α inhibitors on liver disease in nonmalignant liver diseases.

AUTHOR CONTRIBUTIONS

Amir Ajoolabady provided and wrote the draft of the manuscript. Amir Ajoolabady, Neil Kaplowitz, Cynthia Lebeaupin, Guido Kroemer, Randal J. Kaufman, Harmeet Malhi, and Jun Ren significantly contributed to the revising and intellectual evaluation of the manuscript.

CONFLICT OF INTEREST

Dr. Kaplowitz consults for AstraZeneca and DiliSym.

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